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(REV. 9-2001)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER

740-X01-003

TRANSMITTAL LETTER TO THE UNITED STATES  
DESIGNATED/ELECTED OFFICE (DO/EO/US)  
CONCERNING A FILING UNDER 35 U.S.C. 371

U.S. APPLICATION NO. (If known, see 37 CFR 1.5)

10/018398

INTERNATIONAL APPLICATION NO.

PCT/EP00/03817

INTERNATIONAL FILING DATE

27 April 2000

PRIORITY DATE CLAIMED

12 June 1999

TITLE OF INVENTION

UTILIZATION OF A HIGHLY FLUORORINATED OLIGOMERIC ALKANE IN OPHTHALMOLOGY

APPLICANT(S) FOR DO/EO/US

Udo GROSS, Dirk-Henning MENZ, Erhard KEMNITZ, Hans HOERAUF, and Karin KOBUCH

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
  - a. ☐ is attached hereto (required only if not communicated by the International Bureau).
  - b. ☒ has been communicated by the International Bureau.
  - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
  - a. ☒ is attached hereto.
  - b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
  - a. ☐ are attached hereto (required only if not communicated by the International Bureau).
  - b. ☐ have been communicated by the International Bureau.
  - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
  - d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). UNEXECUTED
10. ☒ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

## Items 11 to 20 below concern document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A **FIRST** preliminary amendment.
14. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
15. ☒ A substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. ☒ Other items or information:  
 MARKED-UP SPECIFICATION  
 COPIES OF REFERENCES CITED IN IDS AND COPY OF SEARCH REPORT FROM PCT/EP00/03817  
 POSTCARD  
 EXPRESS MAIL CERTIFICATE

U.S. APPLICATION NO. (if known, see 37 CFR 1.55)

INTERNATIONAL APPLICATION NO.

ATTORNEY'S DOCKET NUMBER

10/018398

PCT/EP00/03817

740-X01-003

21. ☒ The following fees are submitted:**BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):**

Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO. .... **\$1040.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO ..... **\$890.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO ..... **\$740.00**

International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) ..... **\$710.00**

International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) ..... **\$100.00**

**ENTER APPROPRIATE BASIC FEE AMOUNT =****CALCULATIONS PTO USE ONLY**

\$ 890.00

Surcharge of **\$130.00** for furnishing the oath or declaration later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).

\$ 130.00

| CLAIMS                                      | NUMBER FILED | NUMBER EXTRA | RATE              | \$   |
|---|--------------|--------------|-------------------|------|
| Total claims                                | 8 - 20 =     | 0            | x <b>\$18.00</b>  | \$ 0 |
| Independent claims                          | 1 - 3 =      | 0            | x <b>\$84.00</b>  | \$   |
| MULTIPLE DEPENDENT CLAIM(S) (if applicable) |              |              | + <b>\$280.00</b> | \$   |

**TOTAL OF ABOVE CALCULATIONS =** \$ 1020.00

☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.

+

**SUBTOTAL =** \$ 1020.00

Processing fee of **\$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)).

\$

**TOTAL NATIONAL FEE =** \$ 1020.00

Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **\$40.00** per property +

\$

**TOTAL FEES ENCLOSED =** \$ 1020.00

Amount to be refunded: \$

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- a. ☐ A check in the amount of \$ \_\_\_\_\_ to cover the above fees is enclosed.
- b. ☒ Please charge my Deposit Account No. 500601 in the amount of \$ \$1,020.00 to cover the above fees. A duplicate copy of this sheet is enclosed.
- c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 500601. A duplicate copy of this sheet is enclosed.
- d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

**NOTE:** Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

MARTIN FLEIT

Fleit, Kain, Gibbons, Gutman & Bongini P.L.  
520 Brickell Key Drive #A201  
Miami, FL 33131

Tel (305) 536-9020; Fax (305) 536-9022  
Email mfleit@fleitekain.com

SIGNATURE

Martin Fleit By: Paul D. Bianco Reg# 43,500

NAME

16,900

REGISTRATION NUMBER

PATENT

Attorney Docket No.: 740-X01-003

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicants: Udo GROSS *et al.*

Serial No.: New Patent Application; National Stage of PCT No. PCT/EP00/03817

Group Art Unit:

Filed: December 12 2001

Examiner:

For/Title: UTILIZATION OF A HIGHLY FLUORINATED OLIGOMERIC ALKANE IN  
OPHTHALMOLOGY (AS AMENDED)

**PRELIMINARY AMENDMENT**

BOX PCT  
Assistant Commissioner for Patents  
Washington, DC 20231

Dear Sir:

Please amend the above-identified application as follows prior to an examination on the merits and calculation of any fees:

In the Title

Please amend the title as indicated in the substitute specification and marked-up copy of the specification. The title is being amended to correct a typographic error, *i.e.* changing [alkan] to read alkane, which resulted from the WIPO translation.

In the Specification

Please substitute the attached substitute specification for the specification originally filed. A marked-up copy of the specification showing changes is also attached. The substitute specification does not include any new matter.

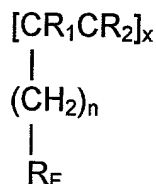
### In the Abstract

Please amend the abstract as indicated in the marked-up copy of the specification and substitute specification. The as-amended abstract does not contain any new matter.

### In the Claims

Please cancel claims 1-7 and add the following new claims:

8. (New) An ophthalmologic treatment agent or pharmacological preparation comprising at least one highly fluorinated alkane of the general formula



wherein

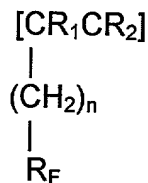
$\text{R}_F$  is a linear or branched perfluorinated alkyl chain  $\text{C}_2\text{F}_5$  to  $\text{C}_{12}\text{F}_{23}$ ,

$\text{R}_1$  and  $\text{R}_2$  are independently selected from the group H,  $\text{CH}_3$ ,  $\text{C}_2\text{H}_5$  and  $\text{C}_3\text{H}_7$ ,

$n$  is selected from the numbers 0, 1 and 2, and

$x$  is a number between 2 and 6,

where a compound of the formula



with a molecular weight of at least 750 was reacted with a radical initiator to a degree of oligomerization of 2 to 6 to produce the highly fluorinated oligomeric alkane.

9. (New) A vitreous body substitute comprising the ophthalmologic treatment agent or pharmacological preparation of claim 8.

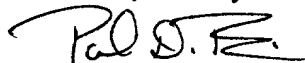
10. (New) A retinal tamponade comprising the ophthalmologic treatment agent or pharmacological preparation of claim 8.

11. (New) A liquid implant comprising the ophthalmologic treatment agent or pharmacological preparation of claim 8.
12. (New) A tear substitute comprising the ophthalmologic treatment agent or pharmacological preparation of claim 8.
13. (New) A carrier substance for pharmacological agents comprising the ophthalmologic treatment agent or pharmacological preparation of claim 8.
14. (New) The ophthalmologic treatment agent or pharmacological preparation of claim 8 wherein the ophthalmologic treatment agent or pharmacological preparation contains a plurality of the highly fluorinated oligomeric alkanes, with each alkane differing from the others.
15. (New) The ophthalmologic treatment agent or pharmacological preparation of claim 8 wherein the ophthalmologic treatment agent or pharmacological preparation is a component of pharmacological preparations for ophthalmology.

#### Remarks

The title has been amended to correct a typographic error. The specification has been amended to add section headings. The abstract has been amended to make it a single paragraph. The claims have been canceled and new claims have been added to conform the claims to United States patent practice and remove multiple dependencies. No new matter has been added.

Respectfully submitted,



Martin Fleit, Reg. #16,900

By: Paul D. Bianco, Reg. #43,500

Martin Fleit  
**FLEIT KAIN GIBBONS GUTMAN & BONGINI**  
520 Brickell Key Drive #A201  
Miami, Florida 33131  
Tel: 305-536-9020; Fax: 305-536-9022  
e-mail: [MFleit@FleitKain.com](mailto:MFleit@FleitKain.com)

PATENT

Attorney Docket No.: 740-X01-003

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicants: Udo GROSS *et al.*

Serial No.: New Patent Application; National Stage of PCT No. PCT/EP00/03817

Group Art Unit:

Filed: December 12 2001

Examiner:

For/Title: UTILIZATION OF A HIGHLY FLUORINATED OLIGOMERIC ALKANE IN  
OPHTHALMOLOGY (AS AMENDED)

**SUBSTITUTE SPECIFICATION**

## UTILIZATION OF A HIGHLY FLUORINATED OLIGOMERIC ALKANE IN OPHTHALMOLOGY

### Field of the Invention

[0001] The invention concerns the utilization of a highly fluorinated oligomeric alkane in ophthalmology.

### Background of the Invention

[0002] U.S. Patent No. 4,490,351 describes the utilization of liquid perfluorocarbons for treatment and diagnosis in ophthalmology. While such substances are used for temporary treatment of retinal detachments and as vitreous body tamponade, their long-term use, for example as vitreous body substitute, is connected with various kinds of injury to the eye. There are known side effects, for example, from perfluoropolyethers and perfluorocarbons, which are due to mechanical injuries at the retina and visual nerve, where the high density (about 1.9 g/cm<sup>3</sup>) of these compounds is blamed for this.

[0003] On the other hand, partially fluorinated liquids that only have a density between 1.1 and 1.3 g/cm<sup>3</sup> and which can be used as auxiliary agents in ophthalmology for retinal unfolding, for vitreous body tamponade and as a vitreous body substitute have been proposed in the publications EP 0 563 446 A1, DE 195 36 504 A1 and DE 197 19 280 A1. These substances, too, in spite of their clearly lower densities, lead to histological changes in the region of the retina and even to the side effects that are otherwise known for perfluorinated carbons.

[0004] Finally, DE 44 05 627 A1 and EP 05 45 174 A1 describe fluorocarbon-containing oligomers of the general formula (R<sub>F</sub>)<sub>x</sub>-R<sub>H</sub> where R<sub>F</sub> means a highly fluorinated alkyl residue, which is bonded directly or via a bonding link to the R<sub>H</sub> group, which stands for an alkane residue or hydrogen and x means a number from 1 to 4, and which are prepared from compounds of the general formula Y-(CF<sub>2</sub>)<sub>a</sub>-O<sub>b</sub>-(CH<sub>2</sub>)<sub>c</sub>-CH=CH<sub>2</sub>, where Y stands for a hydrogen or fluorine atom, a is a number from 2 to 16, and b and c are independently a number between 0 and 1, and d is a number between 0 and 6, with an average degree of oligomerization from 2 to 4. In said publications the described substances are described as being used as greases or lubricants and as ski base materials and also as oxygen carriers.

### Summary of the Invention

[0005] There is the task of providing a pharmacological agent for use in ophthalmology that causes little or no damage to the retina even when used over a long period. This task is solved

through the utilization of a substance as in Claim 1. Advantageous uses and embodiments can be taken from the subordinate claims.

### Detailed Description of the Embodiments

[0006] The idea underlying the invention and forming a part of the invention lies in the fact that the injurious effect of fluorocarbons when used in the eye for long periods of time is essentially caused by their ability to penetrate tissue and by the interaction of their viscosities and high densities. This is true not only when these substances are used as vitreous body substitutes in ophthalmology, but also when they are used as liquid implants, as tear substitutes and as treatment agents for the eye directly or as active agent carriers.

[0007] This idea led to the search for substances with higher viscosity with sufficiently high density and sufficient dissolving power and at the same time only minimum tissue penetration.

[0008] The tissue penetration capacity can be described qualitatively by the critical solubility temperature in hexane (abbreviation: CST). This qualitative measure of lipophilicity is at the same time a measure of the capacity for tissue penetration. While the low molecular  $R_F-R_H$  compounds known from the prior art mentioned above in utilization for ophthalmology as a rule have CST values under  $-20^{\circ}\text{C}$ , the high molecular oligomeric compounds in accordance with the invention are, in contrast, are not completely miscible with hexane until temperatures over  $+35^{\circ}\text{C}$  are reached and thus provide evidence for their insolubility or poor solubility in lipids, thus their low tissue penetration capacity. Surprisingly, in spite of this, they have a dissolving capacity for certain nonpolar substances that is higher than their monomeric analogs.

[0009] The substances in accordance with the invention, because of their particular molecular form, and in spite of their similar chemical composition to the known  $R_F-R_H$  compounds, are not tissue-penetrating and thus suitable for long-term use in the eye, since it was recognized that the tissue-damaging properties of the known substances are due to their high penetration. It is advantageous for ophthalmological applications that the treatment agent used in accordance with the invention, because of the combination of reduced density and elevated viscosity, does not have a mechanically injurious effect in the eye and therefore can be used as a long-term vitreous body substitute. Compared to the silicone oil that is used at the present time, the utilization of the oligomers in accordance with the invention has the advantage that they can be used for coordinated oxygen therapy for the ischemic retina for a simultaneous excellent tamponade effect and can also be used in the lower segment of the eye because of the particular surface properties and their higher density than silicone oil and water.

[0010] For the same reason the utilization of the described oligomers in accordance with the invention enables various other ophthalmological applications that up to now were exclusively reserved to silicone oils. This in particular concerns the utilization as volume replacements, for



example, in the form of implants. Moreover, completely new ophthalmological applications were also possible. With the utilization of the oligomers in accordance with the invention in one particularly viscous embodiment cloudy natural lenses can be replaced. Here the natural lens is extracted while maintaining the surrounding capsule, which is followed by an injection of the highly viscous oligomer into this capsule. The fluid lens materials allow retention of accommodation. Advantageously oligomers with a high degree of branching can be used for this, or the already substantially high viscosity of the oligomers can be increased even further by producing gels through the addition of certain mixtures of water and surface-active substances in accordance with known methods.

**[0011]** In addition, uptake of water-soluble substances into the liquid implants is enabled in this way, which considerably broadens their therapeutic applicability. Thus, with these gels applications have become possible in which it is necessary to have extremely high viscosity (fluid lenses) and mechanical stress on adjacent tissues that is as low as possible, with simultaneous absorption capacity for ions (vitreous body substitute). A really important advantage compared to the conventional fluorocarbons is that even if the gels are degraded, the remaining media can partially maintain the implant effects, since they themselves already have sufficient viscosity.

**[0012]** Utilization as active agent carrier is based on the possibility of dissolving pharmacological agents in the oligomers, where in particular the unusual combination of dissolving capacity on the one hand and reduced tissue penetration on the other is important. For this reason utilization as active agent carriers both in the form of volume replacements and without these application functions is of particular interest.

**[0013]** The advantageous physical properties like oxygen solubility as well as film-forming, but not tissue penetrating action allow other applications for the highly fluorinated oligomers, for example, as tear substitutes.

**[0014]** An important advantage of the described substances in view of the utilization in accordance with the invention is that they combine the known properties of fluorocarbons and silicone oil together, especially the high viscosity of silicone oil and the high density and oxygen dissolving power of fluorocarbons, namely without the toxicities that are known for other substances, for example, fluorosiloxanes or the complicated proportions that are present in mixtures of silicone oil and partially fluorinated alkanes and that limit or exclude their use as treatment agents in ophthalmology.

**[0015]** In addition, the oligomers, when used for ophthalmological purposes, offer the advantage that, in contrast to the silicone oils, they can be removed by simple washing since advantageous biocompatible solvents are available for the perfluorocarbons that had been mentioned for short-term use in ophthalmological practice, for example, perfluorodecalin or

perfluorooctane, but also partially fluorinated alkanes such as  $C_6F_{13}C_2H_5$  or  $C_4F_9C_4H_9$ . On the other hand, if necessary an exchange for silicone oil or vice versa can take place without the compounds mixing together.

[0016] The described oligomeric compounds have a viscous to highly viscous or even paste-like consistency and a density between 1.2 and 1.7 g/cm<sup>3</sup>. They are optically transparent with a refractive index between 1.30 and 1.45. The compounds are essentially nonpolar. However, as a peculiarity compared with the two molecular components alkane and perfluoroalkane, in isolated state there is a weak characteristic molecular polarity due to the  $CF_2-CH_2$  group that is typical of the compounds. Physical properties like molecular weight, density, refractive index, viscosity, optical transparency and dissolving capacity can be varied according to purpose of application. This takes place through the choice of the  $R_F$  and  $R_H$  groups, their degree of branching and the degree of oligomerization. The physicochemical properties, however, can also be adjusted through the addition of perfluorinated or partially fluorinated alkanes. The highly fluorinated oligomers are chemically and thermally extraordinarily stable and are not enzymatically degradable. They are toxicologically and dermatologically safe.

[0017] The preparation and purification of the described substances takes place in a substantially known way. For example, they are obtained as described in DE 41 39 765 or through the reaction of a branched, perfluorinated olefin with potassium or cesium fluoride in an aprotic solvent with an alkenyl halide and oligomerization with a radical initiator in a nonpolar solvent. The purification takes place, for example, by extractive and column chromatographic processes.

[0018] Some embodiment examples of a highly fluorinated oligomer are described in more detail below.

[0019] Example 1

[0020] The highly fluorinated oligomer  $(C_6F_{13}CHCH_2)_3$  is dissolved in fluorocarbons and purified via an  $Al_2O_3$  chromatographic column. After removal of the solvent the last traces of volatile contaminants are removed in a vacuum. The highly fluorinated trimer according to nuclear spin resonance, infrared and mass spectroscopic tests, a uniform and highly pure substance with a molecular weight of 1055. Charging with an active agent takes place under mild conditions via a solvent that is not miscible with the trimer after distribution to saturation concentration.  $\beta$ -Carotene as active agent changes the color of the oligomer slightly. It is sterilized at 121°C in an autoclave, without the physical or chemical properties of the substances being changed. The nuclear magnetic data of this substance are as follows:

$^1\text{H}$ -NMR:  $\text{CH}_3$ : 0.95 ppm;  $-\text{CH}-\text{CF}_2-$ : 2.02 ppm;  $\text{CH}_2-$ : 1.64 ppm

$^{19}\text{F}$ -NMR:  $\text{CF}_3$ : 82.8 ppm;  $-\text{CH}-\text{CF}_2-$ : 116.2 ppm;  $4\text{CF}_2-$ : 123.2 ppm, -124.3 ppm, -124.8 ppm, -127.7 ppm

$^{13}\text{C}$ -NMR:  $\text{CH}_3-/ \text{CH}_2-$ : 25-35 ppm  
 $\text{CF}_3-/ \text{CF}_2-$ : 105-120 ppm

**[0021]** The purity of the substance is essentially characterized by the following physical properties:

Density: 1.661 g/cm<sup>3</sup>;

Refractive index  $n_{20}^D$ : 1.3351;

Surface tension: 19.5 mN/m;

Critical solubility temperature in n-hexane, CST: 35°C;

Viscosity: 220 mPa·sec.

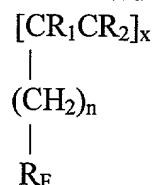
This oligomer is suitable for all of the uses described above and in the claims and has the advantages mentioned above, especially in the area of long-term use.

**[0022]** Example 2

**[0023]** 72 g tridecafluoro-4,4-dimethyl-1-heptene is dissolved in 100 mL n-hexane and oligomerized with 1.7 g di-tert-butyl peroxide at 190°C in an autoclave, resulting in a reaction mixture of a dimeric and trimeric compound. The mixture is separated by distillation, producing the trimer as a viscous colorless oil of the composition  $[\text{CF}_3\text{CF}_2\text{CF}_2\text{C}(\text{CF}_3)_2\text{CH}_2\text{CHCH}_2]_3$  with an average molecular weight of 1085 daltons. According to  $^{19}\text{F}$  and  $^1\text{H}$  NMR as well as infrared spectroscopic tests the compound corresponds to the general formula of the invention and in addition these tests confirm a high degree of purity. According to the relevant in vitro tests the highly fluorinated oil is suitable for the claimed uses.

## Claims

1. Utilization of at least one highly fluorinated alkan of the general formula



where

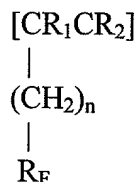
$\text{R}_F$  is a linear or branched perfluorinated alkyl chain  $\text{C}_2\text{F}_5$  to  $\text{C}_{12}\text{F}_{23}$ ,

$\text{R}_1$  and  $\text{R}_2$  are independently selected from the group H,  $\text{CH}_3$ ,  $\text{C}_2\text{H}_5$  and  $\text{C}_3\text{H}_7$ ,

$n$  is selected from the numbers 0, 1 and 2, and

$x$  is a number between 2 and 6,

where a compound of the formula



with the said meanings and with a molecular weight of at least 750 was reacted with a radical initiator to a degree of oligomerization of 2 to 6 to produce the highly fluorinated oligomeric alkane, as a treatment agent in an ophthalmology or pharmacological preparations for ophthalmology.

2. Utilization as in Claim 1 as a vitreous body substitute and/or for retinal tamponade.
3. Utilization as in Claim 1 as a liquid implant.
4. Utilization as in Claim 1 as a tear substitute.
5. Utilization as in Claim 1 as a carrier substance for pharmacological agents that are to be introduced.
6. Utilization as in one of the preceding claims, which is characterized by the fact that the treatment agent contains several of the said highly fluorinated oligomeric alkanes that are different from each other.
7. Utilization as in one of the preceding claims, which is characterized by the fact that the oligomeric alkan is used as a component of pharmacological preparations for ophthalmology and with that in mixtures.

## Abstract

The invention relates to the utilization of a highly fluorinated oligomeric alkane as a therapeutic agent in ophthalmology, the alkane having the general formula  $[-R_F(CH_2)_nCR_1-CR_2-]_x$ , wherein  $R_F$  is a linear or branched perfluorinated alkyl chain  $C_2F_5$  to  $C_{12}F_{23}$ ,  $R_1$  and  $R_2$  are independently selected from the group consisting of H,  $CH_3$ ,  $C_2H_5$  and  $C_3H_7$ ,  $n$  is selected from the numbers 0, 1 and 2, and  $x$  is a number between 2 and 6, with a molar mass of at least 750. According to the invention, a pharmacological agent is provided that is used in ophthalmology and that causes little or no damage to the retina even when used over a long period.

UTILIZATION OF A HIGHLY FLUORINATED OLIGOMERIC ALKAN IN  
OPHTHALMOLOGY

The invention concerns the utilization of a highly fluorinated oligomeric alkan\* in ophthalmology as in Claim 1.

US-A-4,490,351 describes the utilization of liquid perfluorocarbons for treatment and diagnosis in ophthalmology. While such substances are used for temporary treatment of retinal detachments and as vitreous body tamponade, their long-term use, for example as vitreous body substitute, is connected with various kinds of injury to the eye. There are known side effects, for example, from perfluoropolyethers and perfluorocarbons, which are due to mechanical injuries at the retina and visual nerve, where the high density (about 1.9 g/cm<sup>3</sup>) of these compounds is blamed for this.

On the other hand, partially fluorinated liquids that only have a density between 1.1 and 1.3 g/cm<sup>3</sup> and which can be used as auxiliary agents in ophthalmology for retinal unfolding, for vitreous body tamponade and as a vitreous body substitute have been proposed in the publications EP 0 563 446 A1, DE 195 36 504 A1 and DE 197 19 280 A1. These substances, too, in spite of their clearly lower densities, lead to histological changes in the region of the retina and even to the side effects that are otherwise known for perfluorinated carbons.

Finally, DE 44 05 627 A1 and EP 05 45 174 A1 describe fluorocarbon-containing oligomers of the general formula  $(R_F)_x-R_H$  where  $R_F$  means a highly fluorinated alkyl residue, which is bonded directly or via a bonding link to the  $R_H$  group, which stands for an alkan residue or hydrogen and  $x$  means a number from 1 to 4, and which are prepared from compounds of the general formula  $Y-(CF_2)_a-O_b-(CH_2)_c-CH=CH_2$ , where  $Y$  stands for a hydrogen or fluorine atom,  $a$  is a number from 2 to 16, and  $b$  and  $c$  are independently a number between 0 and 1, and  $d$  is a number between 0 and 6, with an average degree of oligomerization from 2 to 4. In said publications the described substances are described as being used as greases or lubricants and as ski base materials and also as oxygen carriers.

There is the task of providing a pharmacological agent for use in ophthalmology that causes little or no damage to the retina even when used over a long period. This task is solved through the utilization of a substance as in Claim 1. Advantageous uses and embodiments can be taken from the subordinate claims.

The idea underlying the invention and forming a part of the invention lies in the fact that the injurious effect of fluorocarbons when used in the eye for long periods of time is essentially caused by their ability to penetrate tissue and by the interaction of their viscosities and high

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\* [Translator's note: sic: alkane; spelling as in English abstract.]

densities. This is true not only when these substances are used as vitreous body substitutes in ophthalmology, but also when they are used as liquid implants, as tear substitutes and as treatment agents for the eye directly or as active agent carriers.

This idea led to the search for substances with higher viscosity with sufficiently high density and sufficient dissolving power and at the same time only minimum tissue penetration.

The tissue penetration capacity can be described qualitatively by the critical solubility temperature in hexane (abbreviation: CST). This qualitative measure of lipophilicity is at the same time a measure of the capacity for tissue penetration. While the low molecular  $R_F-R_H$  compounds known from the prior art mentioned above in utilization for ophthalmology as a rule have CST values under  $-20^{\circ}\text{C}$ , the high molecular oligomeric compounds in accordance with the invention are, in contrast, are not completely miscible with hexane until temperatures over  $+35^{\circ}\text{C}$  are reached and thus provide evidence for their insolubility or poor solubility in lipids, thus their low tissue penetration capacity. Surprisingly, in spite of this, they have a dissolving capacity for certain nonpolar substances that is higher than their monomeric analogs.

The substances in accordance with the invention, because of their particular molecular form, and in spite of their similar chemical composition to the known  $R_F-R_H$  compounds, are not tissue-penetrating and thus suitable for long-term use in the eye, since it was recognized that the tissue-damaging properties of the known substances are due to their high penetration. It is advantageous for ophthalmological applications that the treatment agent used in accordance with the invention, because of the combination of reduced density and elevated viscosity, does not have a mechanically injurious effect in the eye and therefore can be used as a long-term vitreous body substitute. Compared to the silicone oil that is used at the present time, the utilization of the oligomers in accordance with the invention has the advantage that they can be used for coordinated oxygen therapy for the ischemic retina for a simultaneous excellent tamponade effect and can also be used in the lower segment of the eye because of the particular surface properties and their higher density than silicone oil and water.

For the same reason the utilization of the described oligomers in accordance with the invention enables various other ophthalmological applications that up to now were exclusively reserved to silicone oils. This in particular concerns the utilization as volume replacements, for example, in the form of implants. Moreover, completely new ophthalmological applications were also possible. With the utilization of the oligomers in accordance with the invention in one particularly viscous embodiment cloudy natural lenses can be replaced. Here the natural lens is extracted while maintaining the surrounding capsule, which is followed by an injection of the highly viscous oligomer into this capsule. The fluid lens materials allow retention of accommodation. Advantageously oligomers with a high degree of branching can be used for this, or the already substantially high viscosity of the oligomers can be increased even further by

producing gels through the addition of certain mixtures of water and surface-active substances in accordance with known methods.

In addition, uptake of water-soluble substances into the liquid implants is enabled in this way, which considerably broadens their therapeutic applicability. Thus, with these gels applications have become possible in which it is necessary to have extremely high viscosity (fluid lenses) and mechanical stress on adjacent tissues that is as low as possible, with simultaneous absorption capacity for ions (vitreous body substitute). A really important advantage compared to the conventional fluorocarbons is that even if the gels are degraded, the remaining media can partially maintain the implant effects, since they themselves already have sufficient viscosity.

Utilization as active agent carrier is based on the possibility of dissolving pharmacological agents in the oligomers, where in particular the unusual combination of dissolving capacity on the one hand and reduced tissue penetration on the other is important. For this reason utilization as active agent carriers both in the form of volume replacements and without these application functions is of particular interest.

The advantageous physical properties like oxygen solubility as well as film-forming, but not tissue penetrating action allow other applications for the highly fluorinated oligomers, for example, as tear substitutes.

An important advantage of the described substances in view of the utilization in accordance with the invention is that they combine the known properties of fluorocarbons and silicone oil together, especially the high viscosity of silicone oil and the high density and oxygen dissolving power of fluorocarbons, namely without the toxicities that are known for other substances, for example, fluorosiloxanes or the complicated proportions that are present in mixtures of silicone oil and partially fluorinated alkanes and that limit or exclude their use as treatment agents in ophthalmology.

In addition, the oligomers, when used for ophthalmological purposes, offer the advantage that, in contrast to the silicone oils, they can be removed by simple washing since advantageous biocompatible solvents are available for the perfluorocarbons that had been mentioned for short-term use in ophthalmological practice, for example, perfluorodecalin or perfluorooctane, but also partially fluorinated alkanes such as  $C_6F_{13}C_2H_5$  or  $C_4F_9C_4H_9$ . On the other hand, if necessary an exchange for silicone oil or vice versa can take place without the compounds mixing together.

The described oligomeric compounds have a viscous to highly viscous or even paste-like consistency and a density between 1.2 and 1.7 g/cm<sup>3</sup>. They are optically transparent with a refractive index between 1.30 and 1.45. The compounds are essentially nonpolar. However, as a peculiarity compared with the two molecular components alkane and perfluoroalkane, in isolated



state there is a weak characteristic molecular polarity due to the  $\text{CF}_2\text{-CH}_2$  group that is typical of the compounds. Physical properties like molecular weight, density, refractive index, viscosity, optical transparency and dissolving capacity can be varied according to purpose of application. This takes place through the choice of the  $\text{R}_\text{F}$  and  $\text{R}_\text{H}$  groups, their degree of branching and the degree of oligomerization. The physicochemical properties, however, can also be adjusted through the addition of perfluorinated or partially fluorinated alkanes. The highly fluorinated oligomers are chemically and thermally extraordinarily stable and are not enzymatically degradable. They are toxicologically and dermatologically safe.

The preparation and purification of the described substances takes place in a substantially known way. For example, they are obtained as described in DE 41 39 765 or through the reaction of a branched, perfluorinated olefin with potassium or cesium fluoride in an aprotic solvent with an alkenyl halide and oligomerization with a radical initiator in a nonpolar solvent. The purification takes place, for example, by extractive and column chromatographic processes.

Some embodiment examples of a highly fluorinated oligomer are described in more detail below.

#### Example 1

The highly fluorinated oligomer  $(\text{C}_6\text{F}_{13}\text{CH}_2\text{CH}_2)_3$  is dissolved in fluorocarbons and purified via an  $\text{Al}_2\text{O}_3$  chromatographic column. After removal of the solvent the last traces of volatile contaminants are removed in a vacuum. The highly fluorinated trimer according to nuclear spin resonance, infrared and mass spectroscopic tests, a uniform and highly pure substance with a molecular weight of 1055. Charging with an active agent takes place under mild conditions via a solvent that is not miscible with the trimer after distribution to saturation concentration.  $\beta$ -Carotene as active agent changes the color of the oligomer slightly. It is sterilized at  $121^\circ\text{C}$  in an autoclave, without the physical or chemical properties of the substances being changed. The nuclear magnetic data of this substance are as follows:

$^1\text{H-NMR}$ :  $\text{CH}_3$ : 0.95 ppm;  $-\text{CH-CF}_2-$ : 2.02 ppm;  $\text{CH}_2-$ : 1.64 ppm

$^{19}\text{F-NMR}$ :  $\text{CF}_3$ : 82.8 ppm;  $-\text{CH-CF}_2-$ : 116.2 ppm;  $4\text{CF}_2-$ : 123.2 ppm, -124.3 ppm, -124.8 ppm, -127.7 ppm

$^{13}\text{C-NMR}$ :  $\text{CH}_3-/ \text{CH}_2-$ : 25-35 ppm  
 $\text{CF}_3-/ \text{CF}_2-$ : 105-120 ppm

The purity of the substance is essentially characterized by the following physical properties:

Density:  $1.661 \text{ g/cm}^3$ ;

Refractive index  $n_{20}^D$ : 1.3351;

Surface tension: 19.5 mN/m;

Critical solubility temperature in n-hexane, CST: 35°C;

Viscosity: 220 mPa·sec.

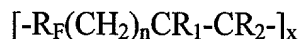
This oligomer is suitable for all of the uses described above and in the claims and has the advantages mentioned above, especially in the area of long-term use.

### Example 2

72 g tridecafluoro-4,4-dimethyl-1-heptene is dissolved in 100 mL n-hexane and oligomerized with 1.7 g di-tert-butyl peroxide at 190°C in an autoclave, resulting in a reaction mixture of a dimeric and trimeric compound. The mixture is separated by distillation, producing the trimer as a viscous colorless oil of the composition  $[\text{CF}_3\text{CF}_2\text{CF}_2\text{C}(\text{CF}_3)_2\text{CH}_2\text{CH}_2\text{CH}_2]_3$  with an average molecular weight of 1085 daltons. According to  $^{19}\text{F}$  and  $^1\text{H}$  NMR as well as infrared spectroscopic tests the compound corresponds to the general formula of the invention and in addition these tests confirm a high degree of purity. According to the relevant in vitro tests the highly fluorinated oil is suitable for the claimed uses.

## Claims

1. Utilization of at least one highly fluorinated oligomer alkan of the general formula



where

$R_F$  is a linear or branched perfluorinated alkyl chain  $C_2F_5$  to  $C_{12}F_{23}$ ,

$R_1$  and  $R_2$  are independently selected from the group H,  $CH_3$ ,  $C_2H_5$  and  $C_3H_7$ ,

$n$  is selected from the numbers 0, 1 and 2, and

$x$  is a number between 2 and 6,

with a molecular weight of at least 750, as a treatment agent in ophthalmology or in pharmacological preparations for ophthalmology.

2. Utilization as in Claim 1 as a vitreous body substitute and/or for retinal tamponade.

3. Utilization as in Claim 1 as a liquid implant.

4. Utilization as in Claim 1 as a tear substitute.

5. Utilization as in Claim 1 as a carrier substance for pharmacological agents that are to be introduced.

6. Utilization as in one of the preceding claims, which is characterized by the fact that the treatment agent contains several of the said highly fluorinated oligomeric alkan that are different from each other.

7. Utilization as in one of the preceding claims, which is characterized by the fact that the oligomeric alkan is used as a component of pharmacological preparations for ophthalmology and with that in mixtures.

# DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name;

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter that is claimed and for which a patent is sought on the invention entitled

## UTILIZATION OF A HIGHLY FLUORINATED OLIGOMERIC ALKAN IN OPHTHALMOLOGY

the specification of which: (check one)

☐ is attached hereto.

☒ was filed  
as International Application No. PCT/EP00/03817  
and was amended on August 14, 2001 (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information material to the patentability of this application in accordance with 37 CFR 1.56.

I hereby claim the benefit of foreign priority under 35 USC 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below any foreign application for patent or inventor's certificate or of any PCT international application having a filing date before that of the application the priority of which is claimed:

| Prior Foreign Application(s): |         |               | Priority Claimed |    |
|-------------------------------|---------|---------------|------------------|----|
| Number                        | Country | Filing Date   | Yes              | No |
| 199 26 890.8                  | DE      | June 12, 1999 | XXX              |    |

I hereby claim the benefit of United States priority under 35 USC 120 of any United States application(s) or 365(c) of any PCT international applications designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is disclosed in a listed one of the prior United States or PCT international application in the manner provided by the first paragraph of 35 USC 112, I

acknowledge the duty to disclose information material to the patentability of this application as defined in 37 CFR 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application: U.S. Parent Application or PCT Parent (Filing Date) Parent Patent Number

Number

PCT/EP00/03817

April 27, 2000

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

|                    |                        |
|--------------------|------------------------|
| Martin Fleit       | Reg. No. <u>16,900</u> |
| Paul D. Bianco     | Reg. No. <u>43,500</u> |
| Robert C. Kain     | Reg. No. <u>30,648</u> |
| Jon A. Gibbons     | Reg. No. <u>37,333</u> |
| Stephen C. Bongini | Reg. No. <u>40,917</u> |
| Jose Gutman        | Reg. No. <u>35,171</u> |

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Send correspondence to MARTIN FLEIT, Fleit, Kain, Gibbons, Gutman & Bongini, P.L., 520 Brickell Key Drive, Miami, Florida 33131, and direct all telephone calls to MARTIN FLEIT at (305) 536-9020.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 USC 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

FULL NAME OF INVENTOR: Udo GROSS

INVENTOR'S SIGNATURE: Udo Gross

DATE: 10.12.01

RESIDENCE: Germany DEX

CITIZENSHIP: Germany

POST OFFICE ADDRESS: Prignitzstrasse 32, D-12683 Berlin, GERMANY

FULL NAME OF INVENTOR: Dirk-Henning MENZ

INVENTOR'S SIGNATURE: Dirk-Henning Menz

DATE: 10<sup>th</sup> Dec 2001

RESIDENCE: Germany DEX

CITIZENSHIP: Germany

POST OFFICE ADDRESS: Wartheweg 12, D-86420 Diedorf, GERMANY

FULL NAME OF INVENTOR: Erhard KEMNITZ 3-00

INVENTOR'S SIGNATURE: Erhard Kemnitz DATE: 8<sup>th</sup> Dec. 2001

RESIDENCE: Germany DEX

CITIZENSHIP: Germany

POST OFFICE ADDRESS: Prenzlauer Allee 218, D-10405 Berlin, GERMANY

FULL NAME OF INVENTOR: Hans HOERAUF 4-00

INVENTOR'S SIGNATURE: H. Hoerauf DATE: 14<sup>th</sup> Dec. 2001

RESIDENCE: Germany DEX

CITIZENSHIP: Germany

POST OFFICE ADDRESS: Gartenweg 15, D-23730 Sierksdorf, GERMANY

FULL NAME OF INVENTOR: Karin KOBUCH 5-00

INVENTOR'S SIGNATURE: Karin Kobuch DATE: 18.12.2001

RESIDENCE: Germany DEX

CITIZENSHIP: Germany

POST OFFICE ADDRESS: Heckenweg 1, D-93080 Pentling, GERMANY